REMARKS

Interview

Applicant's representatives Thomas Turano and James Culverwell thank the examiner for the productive interview on September 23, 2010. During the interview, amendments were discussed that would obviate the non-statutory subject matter rejection. In addition, the cited references were discussed and, specifically, that Applicant's invention uses data from two markers, wherein one marker is non-informative at a first stage of pregnancy but is informative at a second stage while the other marker is informative at a first stage but is non-informative at a second stage.

Status of the claims

Prior to this amendment, claims 1-4, 6, 8, 9, 11, 12, 14-20, 22, 23, 26-27, 32, 40, and 41 were pending in the application. Claims 2, 6, 8, 11, 22, and 25 are cancelled without prejudice. New claims 42-44 are added. Claims 1, 20, and 32 are presently amended to specify that the first biological parameter is PAPP-A and that the second biological parameter is one of total hCG, Inhibin-A, AFP and uE_3. In addition, claims 1, 20, and 32 have been amended to clarify that the first biological parameter has substantially no value as a marker during the second stage of pregnancy and that that second biological marker has substantially no value as a marker during the first stage of pregnancy. Finally, claims 1 and 20 are amended to recite a computer. Support for the amendments to the claims is found in the specification at least, for example at paragraphs 17, 21, 29, 35, 36, and Table 9 of the published application (U.S. 2007/0148631). Thus, upon entry of this amendment, claims 1, 3, 4, 9, 12, 14-20, 23, 26, 27, 32, 40, and 41 will be pending and presented for examination.

Applicant believes that the claim amendments introduce no new matter.

Correction

Applicants would like to correct an erroneous statement made in the previous response submitted on March 1, 2010. In that response it was stated that Davies uses only a single marker. This statement is incorrect. It appears the Examiner also has assumed that Davies teaches using only a single marker. *See* Office action at p.7. Further review of the published

Davies application, EP 0 800 085 A2, shows that Davies mentions on page 4, lines 3-5 that multiple markers can be used. Nevertheless, for the reasons set forth below, Applicant believes the amended claims are patentable over Davies and Nicholls.

Rejections under 35 U.S.C. § 101

Claims 1-4, 6, 8, 9, 11, 12, 14-20, 22, 23, 25-27, 40 and 41 were rejected under 35 USC § 101 as allegedly directed to non-statutory subject matter. Applicant traverses the rejection for the following reasons.

As suggested by the Examiner during the interview, claims 1 and 20 have been amended to recite a computer. Applicant thanks the Examiner for this suggestion and believes that the amended claims now recite sufficient structure.

Accordingly, Applicant submits that independent claims 1 and 20, and the claims dependent therefrom, are directed to statutory subject matter. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection under § 101.

Rejections under 35 U.S.C. § 103(a)

Claims 1-4, 6, 8, 9, 11, 12, 14-20, 22, 23, 25-27, 32, 40 and 41 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over European Patent No. EP 0 800 085 to Davies ("Davies") in view of International Publication No. WO 99/56132 to Wald by agent Nicholls ("Nicholls"). Applicants traverse the rejection for the following reasons.

Independent claims 1, 20, and 32 have been amended to more clearly recite the claimed invention. Specifically, these claims are amended to specify that the first biological parameter is PAPP-A and that the second biological parameter is one of total hCG, Inhibin-A, AFP and uE_3. In addition, these claims have been amended to clarify that the first biological parameter has substantially no value as a marker during the second stage of pregnancy and that that second biological marker has substantially no value as a marker during the first stage of pregnancy. The amended claims read, in relevant part:

> wherein said first biological parameter is a marker for said chromosomal abnormality at the first stage of pregnancy and has substantially no value as a marker during the second stage of pregnancy, and

> wherein said second biological parameter is a marker for said chromosomal abnormality at said second stage of pregnancy and has substantially no value as a marker during the first stage of pregnancy.

It would not be obvious to combine Davies and Nicholls as alleged in the Office action because Nicholls teaches away from their combination. First, in contradistinction to the claimed invention, Nicholls teaches that a marker should be measured only at the stage for which it is useful. For example, Nichols states:

> The present invention utilises the fact that the ability of different screening markers to discriminate between Down's syndrome pregnancies and unaffected pregnancies varies according to the stage of pregnancy. For example, the screening marker PAPP-A is most useful before 14 weeks, but not afterwards, and vice versa with the screening marker inhibin-A, as summarised in Wald NJ, Kennard A, Hackshaw A, McGuire A. (1997); Antenatal screening for Down's syndrome. J Med Screen 4,181-246.

(Nicholls, at p.4, lns. 6-14). Nicholls further instructs that "Any markers which are effective at each particular stage may be selected." (Nicholls, at p.8, lns. 14-15). Thus, Nicholls clearly teaches that markers should not be used during stages for which they are not informative.

In contrast, Applicant has discovered that discriminatory power is significantly improved by measuring markers both at a stage for which each marker is informative *and* at a stage for which each marker provides substantially no informative value. In one comparison the false positive rate for PAPP-A is reduced from 17%, when PAPP-A is measured only in the first trimester, to 1.9% using Applicant's claimed method, for an 85% detection rate. (*See* Applicant's published application (U.S. 2007/0148631), at ¶ 17). Combining the analysis of PAPP-A with that of a second marker which is non-informative in the first trimester and informative in the second trimester (i.e., the inverse of PAPP-A) yields even greater accuracy and stronger discriminatory power. This is demonstrated by Table 9 of Applicant's published application (US2007/0148631) , where PAPP-A measurements combined with measurements of a second marker (total hCG, Inhibin-A and uE_3) yield lower false positive detection rates of 1.0%, 0.8% and 0.5% respectively. This result is unexpected and significant in view of the cited references, which fail to teach or suggest this methodology. As set out in paragraph 0115, the performance of these tests is better than an integrated prior art test that incorporates six features, including NT.

The false positive detection rate may be decreased still further by including NT (as expressed in claims 12 and 27) to bring the rates down to 0.4%, 0.5% and 0.1% respectively. Alternatively, the false positive detection rate may be decreased by including a third biological marker which is another of the second markers (as expressed in new claims 42-44), for example PAPP-A combined with Inhibin-A and uE_3 yields a false positive rate of 0.1%.

Furthermore, Nicholls teaches away from using markers which are highly correlated. While the Office action suggests that using multiple, correlated markers is mere duplication (Office action, p.9), Nicholls nevertheless teaches that correlated markers are to be avoided:

> Preferably, one would not use both free-hCG from the first trimester and total hCG from the second trimester because of an expected high correlation between these markers.

(Nicholls, at p.8, lns. 20-24).

> When using several markers in combination to screen for a particular disorder, it is desirable to take account of correlation between the markers. If two markers are perfectly correlated, one adds nothing to the other in assessing the risk of having the disorder, whereas if they are completely uncorrelated, each provides an independent measure of risk.

(Nicholls, at p.9, lns. 12-14). Thus, according to Nicholls, corroborated markers add little value. Applicant's claimed invention appreciates that it is advantageous to measure markers which are highly correlated with one another at two different gestational ages, because this enables some degree of compensation for natural variations in a marker between subjects.

Additionally, in contrast to either Davies or Nicholls, Applicant's claimed invention can make use of markers that have predictive value at one stage of pregnancy but not at another, further reducing the false positive rate. Although Davies mentions using multiple markers, including some of the claimed markers, Davies is silent with respect to using two markers where one marker is informative at a first stage of pregnancy but is non-informative at a second stage while the other marker is non-informative at a first stage but is informative at a second stage. Furthermore, Davies fails to teach or suggest using the claimed combination of markers.

Accordingly, for at least the reasons given above, Applicant submits that independent claims 1, 20 and 32, and the claims that depend therefrom, are patentable over Davies and Nicholls, either alone or in combination.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that the pending claims are in condition for allowance and therefore request early favorable action by the Examiner.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

Respectfully submitted,

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